

IMPACT OF TIMING OF RENAL REPLACEMENT THERAPY INITIATION ON OUTCOME OF ACUTE KIDNEY INJURY IN SEPTIC PATIENTS

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ABSTRACT

Objective: To identify whether the timing of initiation of continuous renal replacement therapy affects outcome in septic patients with acute kidney injury in term of 28 days mortality.

Study Design: Cross sectional analytical study.

Place and Duration of Study: This research was conducted at department of Anaesthesiology and critical care unit of the Aga Khan University Hospital, Karachi, from Oct 2018 to Jun 2019.

Methodology: The study reviewed all adult patients aged >18 years who developed acute kidney injury after septic shock and required continuous renal replacement therapy in surgical intensive care unit. Considering the value of blood urea nitrogen, patients were classified into two groups. One was in early group that's was defined as blood urea nitrogen value of <100 mg/dl just before continuous renal replacement therapy initiation while the patients who have blood urea nitrogen value of ≥ 100 mg/dl just prior to continuous renal replacement therapy initiation were classified as late group. Kaplan-Meier survival analysis was performed and median survival was computed.

Results: Forty patients were included for analysis. There were thirty patients (75%) in early group in whom continuous renal replacement therapy was started with mean blood urea nitrogen of 66 ± 20.2 mg/dL and 10 (25%) patients were in late group with mean blood urea nitrogen of 137 ± 28.4 mg/dL. The overall survival rates in both groups were 49.6%, and 10.4% at 10 and 25 days, respectively. Median survival time was not statistically significant between early and late continuous renal replacement therapy groups 9 (2.74) vs. 11 (0.41); $p=0.997$.

Conclusion: Septic patients who developed acute kidney injury and started continuous renal replacement therapy did not showed in any mortality benefit among both groups.

Keywords: Acute kidney injury, Intensive care, Renal replacement therapy, Sepsis.

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INTRODUCTION

Acute kidney injury (AKI) is a common and devastating complication of critical illness. It is a common complication of intensive care unit ranging from 6% to 60% despite the technical advances and care in this field of medicine. Mortality remains very high in these group of patients (50% to 63%)¹. One of the studies conducted in Pakistan showed that 31% of patients admitted in critical care suffered AKI during the course of the disease². Acute kidney injury is being one of the independent risk component for mortality and as well as the development of chronic renal failure in patients who suffered AKI in critical care³. The pathophysiology of AKI development after sepsis and septic shock is still unclear, but the leading

cause of AKI in critically ill patients is sepsis and septic shock. Treatment of acute kidney injury is only supportive, most of the patient treats conservatively and interventions have not been benefit for restoration of renal function so it will not improve overall survival. Conventional hemodialysis requires hemodynamic stability. A lot of patients in intensive care units (ICU) are in septic shock and have unstable hemodynamics due to which they cannot undergo conventional dialysis. These patients can only benefit from continuous renal replacement therapy (CRRT). Severe AKI is mostly treated with specific modalities of hemodialysis that is continuous renal replacement therapy. If renal replacement therapy imitation started late then in-hospital mortality of such patients may exceeds up to 50%. Early initiation of CRRT may be beneficial and improve survival that is explained by a recent meta-analysis, but most of

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the data were derived from observational studies⁴. The review of the literature did not clearly explain the optimal time of continuous renal replacement therapy initiation in order to get maximum benefit in term of survival⁵. It is almost ten years that we have started CRRT at our center. This study helps us to find out the true efficacy of CRRT on our settings. Serum blood urea nitrogen (BUN) can be surrogate marker to early versus late initiation of continuous renal replacement therapy. The purpose of this study was to identify retrospectively whether the timing of initiation of continuous renal replacement therapy (CRRT) affects outcome in septic patients with acute renal failure (ARF) in term of 28 days mortality.

METHODOLOGY

Our hospital was commissioned in 1985. In 2009, the hospital had started CRRT in intensive care unit. Nephrologist and Intensivists were assigned for initiation of CRRT. The mechanism of data reporting is through electronic records by HIMS. We followed the departmental and hospital policy for access and referral of data. Ethical approval was obtained from the Ethics Review Committee of our University (Ref No: 2018-0430-595 Dated October 22nd, 2018). We reviewed all patients who were admitted in Surgical ICU between 2009 to 2018 (10 years) with diagnosis of sepsis, severe sepsis and septic shock and developed acute kidney injury requiring CRRT. We designed a specific performa for the purpose of this audit. Patients who have CRRT duration less than 24 hours and having incomplete data were excluded. Patients, anesthesiologist, primary physician and nurse' identification were not disclosed on the data collection form. Patient demographic details, comorbid, laboratory and clinical outcome data of patients who developed AKI and received CRRT as renal replacement therapy were noted. Considering the value of BUN we have classified patients into two groups. One was early group that's was defined as BUN value of <100 mg/dl just before the start of CRRT while the patients with BUN value of ≥100 mg/dl just prior to CRRT initiation were classified as Late group⁶. AKI was defined on the basis of AKIN

(Acute Kidney Injury Network) criteria⁷. The definitions of the terms sepsis, severe sepsis and septic shock were taken from the society of critical care medicine criteria for the sepsis, severe sepsis and septic shock⁸. Admission glasgow coma scale (GCS) were noted while acute physiology and chronic health evaluation (APACHE II) were calculated after 24 hours of admission. Other clinical parameters like urine output, 24 hours fluid balance just before start of RRT and vital signs on day of RRT initiation were noted. Primary outcome was the 28-day mortality following the start of RRT while secondary outcome were hospital length of stay (days) and duration of CRRT. Both outcomes were determined.

Data was analyzed by Statistical packages for social science version 20. Point estimation of statistics were reported in term of frequency, percentage, mean, standard deviation median survival according to quantitative and qualitative variables. Continuous and normally distributed variables were analyzed by student's t-test to compare mean difference between the groups while Mann-Whitney tests for non-normal data. Chi square test or fisher exact test was used to compare proportion difference between. Kaplan-Meier survival analysis was performed and median survival was computed. In all instances, the level of statistical significance was set at 0.05.

RESULTS

A total of 46 patients were enrolled, who were admitted to the surgical intensive care unit with acute renal failure after septic shock requiring renal replacement therapy. Forty patients were selected for the analysis; Six patient were excluded due to missing data. The mean age of the patients was 55.30 ± 15.91 years (range: 28-81). There were 26 (65%) male and 14 (35%) female. Thirty patients (75%) with mean BUN value of 66 ± 20.2 mg/dL received early CRRT while only 10 patients (25%) with BUN greater than 100 received late CRRT. The demographic characteristics of two groups are shown in table-I. The clinical parameters and laboratory data were comparable before the start of CRRT between the two groups

as shown in table-II. Twenty-four hours urine output just prior to CRRT initiation was lower in the patients who had “early” CRRT initiation but statistically not significant. Between the two groups, no difference was found in APACHI II and Glasgow coma scale as shown in table-II. Mean Blood pressure, heart rate (HR) and respi-

In our study we were focusing on 28 days mortality between the early and late CRRT group but none of our patient survived beyond 25 days. The overall survival rates in both groups were 49.6%, and 10.4% at 10 and 25 days, respectively as shown in the figure. Median survival time was not statistically significant between early and

Table-I: Demographic characteristics of patients.

Variables	Early (BUN<100 mg/dL), n=30	Late (BUN>100 mg/dL), n=10	p-value
Age (Years)	51.47 ± 15.53	66.80 ± 11.14	0.007
Gender			
Male	20 (66.7%)	6 (60%)	0.702
Female	10 (33.3%)	4 (40%)	
Pre-existent conditions	14 (46.7%)	8 (80%)	0.067
Diabetes Mellitus	7 (23.3%)	3 (30%)	0.673
Hypertension	8 (26.7%)	4 (40%)	0.426
IHD	6 (20%)	4 (40%)	0.206
Others	6 (20%)	6 (60%)	0.017

Results are presented as mean ± SD and frequency (%).

Table-II: Clinical and laboratory parameter before crrt.

Variables	Early (BUN<100 mg/dL), n=30	Late (BUN>100 mg/dL), n=10	p-value
APACHI.II	21.20 ± 8.57	26.80 ± 3.05	0.052
GCS on Admission	13.13 ± 2.58	11.20 ± 2.74	0.050
Creatinine Admission (mg/dl)	2.64 ± 1.75	5.64 ± 5.35	0.010
Fluids Admission 24hours	2760 ± 1011.52	2130 ± 616.53	0.072
Hospital days of CRRT	5.43 ± 6.85	6.60 ± 5.72	0.631
Urine Output	303 ± 277.29	205 ± 134.26	0.292
Net Fluid balance	2740 ± 1046.37	2270 ± 749.89	0.199
BUN prior CRT (mg/dl)	53.20 ± 23.33	124.10 ± 19.35	0.001
Serum Creatinine prior (mg/dl)	3.42 ± 2.24	6.57 ± 2.34	0.001
Heart rate (Beats/min)	112.17 ± 16.54	109.50 ± 15.71	0.658
Mean blood pressure (mmHg)	64.67 ± 12.38	62.60 ± 12.83	0.653
Respiratory Rate (Breaths/min)	25.80 ± 6.71	29.40 ± 6.11	0.142
Vasopressor §	26 (86.7%)	10 (100%)	0.224

Results are presented as mean ± SD and n(%)

ratory rate all were not statistically associated between the two groups. Hospital length of stay was little bit more in early group (13.83 ± 13.66) as compare to late (12.70 ± 8.73) but also not statistically significant (p -value=0.81). Hospital days of CRRT duration in days were almost identical between the two groups with p -value of 0.63 as shown in table-II. CRRT duration in days was also high in early group (3.50 ± 2.1) as compare to late (2.70 ± 1.34) with p -value of 0.267 as shown in table-III.

late CRRT groups 9 (2.74) vs. 11 (0.41); p =0.997. Survival rate in the “early” CRRT group was 70% and 16.7% at 10, and 25 days, respectively. The survival rates for the patients in the “late” CRRT group were 57.1%, 11.5% at 10 days and 25 days respectively as shown in figure.

DISCUSSION

Septic shock along with renal failure is associated with high mortality in critically ill patients.

Several clinical efforts were done to determine ways to pick early deterioration in renal function so that clinical outcomes can be improved⁹. There are a lot of anabolic and catabolic phenomena associated with end stage renal disease and these complicated metabolic derangements are treated by CRRT. Initiation of CRRT is associated with a lot of other factors that's including the patient's demographic data, socio-economic status, and clinical conditions^{10,11}. The question about to initiate dialysis in patient with AKI is still in debates, almost as long as

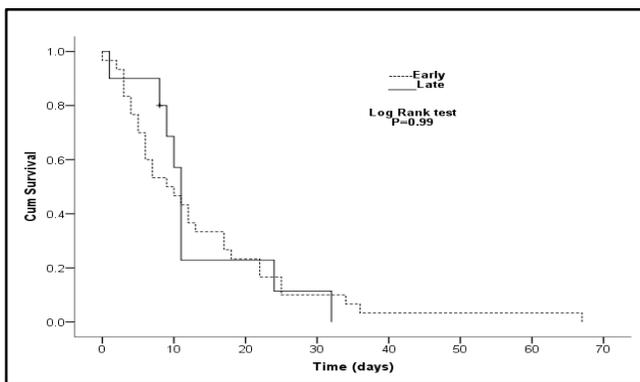


Figure: Kaplan-meir estimate of survival.

hemodialysis has been an integral part for treating patients with AKI in clinical medicines. Determining precise guidelines for commencing CRRT in patients with AKI is imperative; starting too early can lead to unnecessary risk associated with dialysis while on the other hand delayed treatment can have adverse outcomes. Hence clinical practices vary among the clinicians, so it has been too hard to decide when to initiate CRRT. RRT was initiated prophetically in 1950s. In 1960s and 1970s the literature showed that the quick beginning of RRT can improve survival¹². Similar research data had been given in 2000s in cardiac surgery¹³, and oliguric septic patients¹¹. Park *et al*, published prospective cohort study in 2016 showing the survival benefit in critically ill patients with AKI receiving early renal replacement therapy during the course of the disease¹¹. In these different retrospective studies analyses the timing of the start of CRRT. BUN having delegated attention for the marker for the CRRT initiation by most of the studies, but only BUN is

inadequate for assessing the renal function. It doesn't only affected by glomerular filtration rate but also by other mechanism like renal tubular function, protein intake and catabolism, numerous other important clinical situations like gastrointestinal bleeding and drugs¹⁴.

In this study, we determined the outcomes of CRRT in adult patients based on BUN value just prior to CRRT initiation. The results did not indicate a survival benefit of early CRRT initiation. Same findings are observed by prospective and retrospective studies done previously among critical ill patients in intensive care units requiring renal replacement therapy. Systematic review published in 2016 by Raymond *et al*, showed that no survival advantage was found with "early" RRT among high-quality studies with an OR of 0.665 (95% CI 0.384-1.153, $p=0.146$)¹⁷. Jee *et al*, conducted study (REANL study) in 2014 showing that earlier commencement of continuous renal replacement therapy was not associated with a significantly lower risk of death at 28 days¹⁵. Similar findings were observed in most of the studies showing no survival benefit with early CRRT¹⁵⁻²⁰.

On the contrary there are studies showing survival benefit with early renal replacement therapy. Most of the retrospective studies argued that there is an increased survival rate association with early initiation of CRRT^{6,21,22}. The study done by Carl *et al*⁶, included retrospective data on medical intensive care unit patients with sepsis and acute renal failure requiring renal replacement therapy. Renal replacement therapy started with a blood urea nitrogen (BUN) of <100 mg/dL was defined as "early" initiation, and initiation with a BUN ≥ 100 mg/dL was defined as "late" Upon logistic regression analysis, initiating dialysis with a BUN >100 mg/dL predicted death at 14 days (odds ratio [OR] 3.6, 95% confidence interval [CI] 1.7-7.6, $p=0.001$), 28 days (OR 2.6, 95% CI 1.2-5.7, $p=0.01$), and 365 days (OR 3.5, 95% CI 1.2-10, $p=0.02$). The study showed that septic patients who started on dialysis with BUN less than 100 mg/dl had improved mortality rates.

In this study our all patients were in septic shock no one was in sepsis or in severe sepsis so our patients were more critically ill, in some previous retrospective studies severity of recruited patient were not too high^{16,18}, this is the one of major strength of our study. According to the KDIGO Clinical Practice Guideline for acute kidneyinjury, the timingof RRT initiation was not clearly described it is dependent upon clinician's clinical decisions. So every author haphazardly defined early and late CRRT. In spite of the fact that RRT those started early may have better survival rate, but it is hard to suggest the proper timing for CRRT initiation. There are several limitations in this observational study. First, we didn't measure detail parameters of CRRT like choice and method of CRRT because in our study we have included very high-riskpatients those who were already in septic shock, so it was not easy to measure the detailed parameters of CRRT. On the contrary, it is also important to determine the modality of CRRT as it would be better considering the risks and benefits, clinically. Second, the sample size of this study was small and from one institute, so we could not generalize our results to various patient populations. There is need of some multicenter prospective study for future validation. Lastly, we did not analyze the specific indication for initiation of CRRT in septic patients with AKI. The reason of initiation of CRRT may have an impact on the prognosis of septic shock patients with AKI. The start of CRRT cannot be based on few variables; rather the whole clinical picture of patient is important in initiating the CRRT. In this study we tried to identify whether early or late initiation of CRRT in septic patients with AKI have any impact on mortality, but our study showed no difference between the two groups. There are limitations of this study which include small sample size and retrospective nature of study. Large prospective trails are needed to validate this study results.

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CONCLUSION

No significant difference was found in patients' outcome who were put on CRRT for sepsis induced acute kidney injury. Timing of continuous renal replacement therapy (CRRT) does not affect the mortality in patient with AKI on basis of BUN value.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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